Complete Summary

GUIDELINE TITLE

National High Blood Pressure Education Program: Working Group report on high blood pressure in pregnancy.

BIBLIOGRAPHIC SOURCE(S)

National Heart Lung and Blood Institute. National High Blood Pressure Education Program: Working Group Report on High Blood Pressure in Pregnancy. Bethesda (MD): National Heart, Lung and Blood Institute (NHLBI); 2000 Jul. 38 p. [201 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Hypertension in pregnancy
- Preeclampsia

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Prevention
Treatment

CLINICAL SPECIALTY

Anesthesiology
Family Practice

Internal Medicine
Obstetrics and Gynecology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To provide guidance to practicing clinicians on managing (1) patients with hypertension who become pregnant and (2) patients who develop hypertensive disorders during gestation
- To update contemporary approaches to hypertension control during pregnancy by expanding on recommendations made in the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

TARGET POPULATION

Pregnant women with hypertension

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Laboratory tests for differential diagnosis and/or management, including:
    - Hemoglobin and hematocrit, platelet count, blood smear, and coagulation profile
    - Quantification of protein excretion
    - Serum creatinine, uric acid, transaminase, albumin, and lactic acid dehydrogenase levels
2. The use of Korotkoff 5 (K5) for determining diastolic pressure
   Note: Edema as a diagnostic indicator of preeclampsia was considered but not recommended. In addition, the use of blood pressure increases of 30 mm Hg systolic or 15 mm Hg diastolic as a diagnostic criterion for preeclampsia was considered but not recommended, based on available evidence.
3. Assessment of fetal size, growth, and well-being in chronic hypertension, gestational hypertension and preeclampsia, including:
    - Initial sonographic assessment of fetal size and dating at 18 to 20 weeks gestation
    - Fundal height and/or sonographic assessment of fetal growth
    - Ultrasound assessment of fetal activity and amniotic fluid status
    - Nonstress tests and biophysical profiles
    - Daily fetal movement assessment/counts
    - Amniocentesis

Prevention

1. Low-dose aspirin, calcium, and/or other dietary supplementation to prevent preeclampsia.

Management

1. Treatment of chronic hypertension
    - Treatment of women with Stage 1 to 2 chronic hypertension (non-drug therapy)
    - Treatment to prevent the exacerbation of chronic hypertension to severe hypertension (methyldopa [first line therapy], beta-blockers, labetalol, calcium antagonists, diuretics)
    - Treatment of hypertension combined with renal disease (sodium restriction, use of loop diuretics, dialysis)
    - Treatment of hypertension postpartum (oral antihypertensive agents)
    - Treatment of hypertension during lactation
      Note: Angiotensin-converting enzyme inhibitors are considered but not recommended for treatment during pregnancy or while breastfeeding.
2. Management of preeclampsia
    - Nonpharmacologic management including fetal evaluation and maternal evaluation
    - Pharmacologic treatment including hydralazine, labetalol, and nifedipine
      Note: Sodium nitroprusside is considered but not generally recommended.
    - Delivery
3. Anticonvulsive therapy in women with eclampsia or to prevent convulsions in women with preeclampsia
4. Invasive hemodynamic monitoring in select women
5. Prepregnancy and postpartum counseling
6. Counseling for future pregnancies
7. Follow-up

MAJOR OUTCOMES CONSIDERED

- Maternal, fetal, and perinatal morbidity and mortality due to preeclampsia and hypertensive disorders during pregnancy
- Fetal and maternal complications of treatment

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review
Review of Published Meta-Analyses

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Excerpted by the National Guideline Clearinghouse (NGC).

The types of evidence symbols are defined at the end of the "Major Recommendations" section.

I. Classification of the Hypertensive Disorders of Pregnancy

The most important consideration in the classification of diseases in which blood pressure rises abnormally is differentiating hypertensive disorders that

antedate pregnancy from preeclampsia. The editors of the 1990 version of the original guideline document elected to modify minimally the criteria presented by the American College of Obstetricians and Gynecologists (ACOG) Committee on Terminology in 1972. This decision was prompted by the opinion that this classification was simple and used widely and that much of what was understood about the prevalence of these disorders and their outcomes was based on data generated with this classification. The opinion held in the current guideline document, is largely the same.

Several groups, including the American College of Obstetricians and Gynecologists, the Australasian Society for the Study of Hypertension in Pregnancy, and the Canadian Hypertension Society, have published classification schemes and diagnostic criteria that differ from one document to the other and contrast with those presented below. They include recommendations to eliminate edema from diagnostic criteria, to abandon the use of changes in blood pressure as diagnostic, to use only diastolic pressures, and to add systemic changes to proteinuria as diagnostic markers. Of these, the authors of the current guideline document determined that only the elimination of edema and changes in blood pressure as diagnostic criteria can be justified on the basis of available data. There were also differences in designating the Korotkoff sound that determines diastolic blood pressure–K4, muffling or K5, disappearance. The developers chose K5 because substantial data now support its use.

In chronic hypertension, elevated blood pressure is the cardinal pathophysiologic feature, whereas in preeclampsia, increased blood pressure is important primarily as a sign of the underlying disorder and is a potential cause of maternal morbidity. The developers of the current guideline modified the American College of Obstetricians and Gynecologists classification slightly by adding the term "gestational hypertension" for the woman who has hypertension without proteinuria during pregnancy, reserving "transient hypertension" for a definitive diagnosis made postpartum. Women with increased blood pressure are divided into the following groups:

A. Chronic hypertension. Hypertension that is present and observable before pregnancy or that is diagnosed before the 20th week of gestation. Hypertension is defined as a blood pressure equal to or greater than 140 mm Hg systolic or 90 mm Hg diastolic. Hypertension that is diagnosed for the first time during pregnancy and that does not resolve postpartum is also classified as chronic hypertension.
B. Preeclampsia-eclampsia. A pregnancy-specific syndrome that usually occurs after 20 weeks of gestation (or earlier with trophoblastic diseases such as hydatidiform mole or hydrops). It is determined by increased blood pressure (gestational blood pressure elevation) accompanied by proteinuria. Gestational blood pressure elevation is defined as a blood pressure greater than 140 mm Hg systolic or 90 mm Hg diastolic in a woman normotensive before 20 weeks. In the absence of proteinuria the disease is highly suspect when increased blood pressure appears accompanied by the symptoms of headache, blurred vision, and abdominal pain, or with abnormal laboratory tests, specifically, low platelet counts and abnormal liver enzymes.

In the past it has been recommended that an increment of 30 mm Hg systolic or 15 mm Hg diastolic blood pressure be used as a diagnostic criterion, even when absolute values are below 140/90 mm Hg. This definition has not been included in the current guideline because the only available evidence shows that women in this group are not likely to suffer increased adverse outcomes. Nonetheless, it is the collective clinical opinion of the guideline panel that women who have a rise of 30 mm Hg systolic or 15 mm Hg diastolic blood pressure warrant close observation, especially if proteinuria and hyperuricemia (uric acid greater than or equal to 6 mg/dL) are also present.

Diastolic blood pressure is determined as the disappearance of sound (Korotkoff 5). Measuring the blood pressure successively may result in very different readings. It is recommended that gestational blood pressure elevation be defined on the basis of at least two determinations. The repeat blood pressure should be performed in a manner that will reduce the likelihood of artifact and/or patient anxiety. For database studies, the measurements of increased blood pressure should be no more than 1 week apart.

Proteinuria is defined as the urinary excretion of 0.3 g protein or greater in a 24-hour specimen. This will usually correlate with 30 mg/dL ("1+dipstick") or greater in a random urine determination with no evidence of urinary tract infection. However, because of the discrepancy between random protein determinations and 24-hour urine protein in preeclampsia (which may be either higher or lower) it is recommended that the diagnosis be based on a 24-hour urine if at all possible or a timed collection corrected for creatinine excretion if this is not feasible.

Preeclampsia always presents potential danger to mother and baby. Other conditions may increase blood pressure and even result in proteinuria; thus, as the certainty of the diagnosis increases, the requirements for careful assessment and consideration for delivery also increase. The following findings increase the certainty of the diagnosis of the preeclampsia syndrome and indicate such follow-up:

- Blood pressure of 160 mm Hg or more systolic, or 110 mm Hg or more diastolic.
- Proteinuria of 2.0 g or more in 24 hours (2+ or 3+ on qualitative examination). The proteinuria should occur for the first time in pregnancy and regress after delivery.
- Increased serum creatinine (>1.2 mg/dL unless known to be previously elevated).
- Platelet count less than 100,000 cells/mm3 and/or evidence of microangiopathic hemolytic anemia (with increased lactic acid dehydrogenase).
- Elevated hepatic enzymes (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]).
- Persistent headache or other cerebral or visual disturbances.
- Persistent epigastric pain.

Eclampsia is the occurrence, in a woman with preeclampsia, of seizures that cannot be attributed to other causes.

Edema occurs in too many normal pregnant women to be discriminant and has been abandoned as a marker in this and other classification schemes.

C. Preeclampsia superimposed upon chronic hypertension. There is ample evidence that preeclampsia may occur in women already hypertensive (i.e., who have chronic hypertension) and that the prognosis for mother and fetus is much worse than with either condition alone. Distinguishing superimposed preeclampsia from worsening chronic hypertension tests the skills of the clinician. For clinical management, the principle of high sensitivity and unavoidable overdiagnosis is appropriate. The suspicion of superimposed preeclampsia mandates close observation, with delivery indicated by the overall assessment of maternal-fetal well-being rather than any fixed end point. The diagnosis of superimposed preeclampsia is highly likely with the following findings:
    - In women with hypertension and no proteinuria early in pregnancy (<20 weeks), new-onset proteinuria, defined as the urinary excretion of 0.3 g protein or greater in a 24 hour specimen.
    - In women with hypertension and proteinuria before 20 weeks' gestation.
    - Sudden increase in proteinuria
    - A sudden increase in blood pressure in a woman whose hypertension has previously been well controlled.
    - Thrombocytopenia (platelet count <100,000 cells/mm^3)
    - An increase in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) to abnormal levels.

D. Gestational hypertension: (1) transient hypertension of pregnancy if preeclampsia is not present at the time of delivery and blood pressure returns to normal by 12 weeks postpartum (a retrospective diagnosis) or (2) chronic hypertension if the elevation persists. The woman who has blood pressure elevation detected for the first time after midpregnancy, without proteinuria, is classified as having gestational hypertension. This nonspecific term includes women with the preeclampsia syndrome who have not yet manifested proteinuria as well as women who do not have the syndrome. The hypertension may be accompanied by other signs of the syndrome, which will influence management. The final differentiation that the woman does not have the preeclampsia syndrome is made only postpartum. If preeclampsia has not developed and blood pressure has returned to normal by 12 weeks postpartum, the diagnosis of transient hypertension of pregnancy can be assigned. If blood pressure elevation persists, the woman is diagnosed as having chronic hypertension. Note that the diagnosis of gestational hypertension is used during pregnancy only until a more specific diagnosis can be assigned postpartum.

Clinical Implications of Classification

The clinical spectrum of preeclampsia ranges from mild-to-severe forms. In most women, progression through this spectrum is slow, and the disorder may never proceed beyond mild preeclampsia. In others, the disease progresses more rapidly, changing from mild to severe in days or weeks. In the most serious cases, progression may be fulminant, with mild preeclampsia evolving to severe preeclampsia or eclampsia within days or even hours. Thus, for clinical management, preeclampsia should be overdiagnosed, because a major goal in managing preeclampsia is the prevention of maternal and perinatal morbidity and mortality, primarily through timing of delivery.

II. Differential Diagnosis

Decisions regarding hospitalization and delivery that have significant impact on maternal and fetal health are often based on whether the patient is believed to have preeclampsia or a more benign form of high blood pressure, such as chronic or gestational hypertension. The correct diagnosis is important when counseling patients regarding future pregnancies. (See the "Prepregnancy Counseling" section below.)

The period in gestation when hypertension is first documented is helpful in determining the correct diagnosis. Documentation of hypertension before conception, or before gestational week 20, favors a diagnosis of chronic hypertension (either essential or secondary). High blood pressure presenting at midpregnancy (weeks 20 to 28) may be due either to early preeclampsia (rare before 24 weeks), transient hypertension, or unrecognized chronic hypertension. Concerning the latter, blood pressure normally falls in the initial trimesters, and this "physiologic" decrement may even be exaggerated in patients with essential hypertension, masking the diagnosis in pregnancy. Hypertension may be noted later in pregnancy, however, as part of the normal third trimester rise in blood pressure or when superimposed preeclampsia occurs.

Laboratory Tests

Laboratory tests recommended to diagnose or manage hypertension in pregnancy serve primarily to distinguish preeclampsia from either chronic or transient hypertension. They are also useful in assessing the severity of disease, particularly in the case of preeclampsia, which is usually associated with laboratory abnormalities that deviate significantly from those of normal pregnant women. These same measurements are usually normal in women with uncomplicated chronic or transient hypertension.

Efforts to identify an ideal screening or predictive test for preeclampsia have not been successful to date. Several parameters, such as midpregnancy blood pressure, ambulatory blood pressure monitoring, serum beta-human chorionic gonadotropin (beta-hCG), AII sensitivity, urinary calcium excretion, urinary kallikrein, uterine artery Doppler, plasma fibronectin, and platelet activation, have been shown to be statistically valid early markers of disease; however, they have not been demonstrated to have sufficient predictive value or practical utility for application to individual patients.

High-Risk Patients Presenting with Normal Blood Pressure

Pregnant women whose gestations are considered "high risk" for preeclampsia (e.g., history of increased blood pressure before conception or in a previous gestation, especially before week 34, or when the subject is multiparous; women with diabetes, collagen vascular disease, or underlying renal vascular or renal parenchyma disease; and those with a multifetal pregnancy) will benefit from a database of laboratory tests performed in early gestation. Tests that by later comparison will help establish an early diagnosis of preeclampsia (pure or superimposed) include hematocrit, hemoglobin, and platelet count as well as serum creatinine and uric acid levels. Observation of 1 plus protein by routine urine analysis, documented by a clean-catch specimen, should be followed by a 24-hour collection for measurement of protein as well as creatinine content (to determine accuracy of collection and to permit calculation of the creatinine clearance). High-risk patients require accurate dating and assessment of fetal growth. If conditions are not optimal for clinical dating, sonographic dates should be established as early in pregnancy as possible. A baseline sonogram for evaluating fetal growth should be considered at 25 to 28 weeks in these circumstances.

Patients Presenting with Hypertension Before Gestation Week 20

Most women presenting with hypertension before gestation week 20 have, or will develop, essential hypertension; their management is discussed in the next section. (See "Chronic Hypertension In Pregnancy.") Some may be already under the care of primary physicians and screened for secondary hypertension. Young women with preexisting or early gestational hypertension are among the population in which secondary hypertension is more apt to be found (e.g., renal disease, renovascular hypertension, primary aldosteronism, Cushing syndrome, and pheochromocytoma). Thus, further evaluation with noninvasive testing may be warranted, especially when there is suspicion of those forms of secondary hypertension that are associated with more maternal and fetal complications.

The same database described above (high-risk women presenting with normal blood pressure) is helpful in determining whether further increments in pressure in the third trimester represent the "physiologic" increments or the onset of superimposed preeclampsia. Since these fetuses are higher risk for the development of intrauterine growth restriction, early baseline sonography for dating and fetal size is also indicated for these patients.

Patients Presenting with Hypertension After Midpregnancy

Table 1 below summarizes the laboratory tests that are recommended in the evaluation of women with hypertension after midpregnancy and the rationale for testing them biweekly or more often if clinical circumstances lead to hospitalization of the patient. Not only do such tests help to distinguish preeclampsia from chronic and transient hypertension, but they are useful in assessing disease progression and severity. It is important to recognize that in women with preeclampsia, one or more abnormalities may be present even when blood pressure elevation is minimal. If there is a life-threatening abnormality such as coagulopathy or abnormal hepatic or renal function, it may be necessary to terminate the pregnancy despite only mild hypertension. (See the section on "Management of Preeclampsia" below.)

Table 1. Laboratory Evaluation and its Rationale for Women Who Develop Hypertension After Midpregnancy*	
Test	Rationale
Hemoglobin and hematocrit	Hemoconcentration supports diagnosis of pre is an indicator of severity. Values may be dec however, if hemolysis accompanies the diseas
Platelet count	Thrombocytopenia suggests severe preeclamp
Quantification of protein excretion	Pregnancy hypertension with proteinuria shou considered preeclampsia (pure or superimpos proved otherwise.
Serum creatinine level	Abnormal or rising serum creatinine levels, es association with oliguria, suggest severe pree
Serum uric acid level	Increased serum uric acid levels suggest the preeclampsia.
Serum transaminase levels	Rising serum transaminase values suggest se preeclampsia with hepatic involvement.
Serum albumin, lactic acid dehydrogenase, blood smear, and coagulation profile	For women with severe disease, these values extent of endothelial leak (hypoalbuminemia) hemolysis (lactic acid dehydrogenase level inc schizocytosis, spherocytosis), and possible co including thrombocytopenia.

III. Chronic Hypertension in Pregnancy

Prepregnancy Counseling

Women with hypertension should be evaluated before pregnancy to define the severity of their hypertension and to facilitate planning for potential lifestyle changes that a pregnancy may require. As recommended in the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (Type of Evidence: Pr), the diagnosis should be confirmed by multiple measurements and may incorporate home or other out-of-office blood pressure readings. If hypertension is confirmed and particularly if it is severe (stage 3: systolic pressure $\geq$180 mm Hg or diastolic pressure $\geq$110 mm Hg), a woman should be evaluated for potentially reversible causes. Angiotensin-converting enzyme inhibitors and AII receptor antagonists should be discontinued. (For a discussion of drug therapy, see the next section – "Treatment of Chronic Hypertension.")

Women with a history of hypertension for several years should be evaluated for target organ damage including left ventricular hypertrophy, retinopathy, and renal disease. If damage is present, the woman should be advised that pregnancy may exacerbate the condition. Women with chronic hypertension are at higher risk for adverse neonatal outcomes independent of the development of preeclampsia, if proteinuria is present early in pregnancy (Type of Evidence: F). The risks of fetal loss and accelerated deterioration of maternal renal disease are increased if serum creatinine is above 1.4 mg/dL at conception, although it may be difficult to separate the effects of the pregnancy from progression of the underlying renal disease (Type of Evidence: F). In patients with impaired renal function, relative risk of fetal loss has been reported to be increased tenfold when hypertension is present and not controlled at conception, compared with pregnancy without hypertension or with well-controlled hypertension (Type of Evidence: F, Re).

Chronic hypertension before pregnancy requires planning for lifestyle changes. For example, pregnant women with hypertension may need to restrict their activities at work and home and refrain from vigorous exercise. Although regular exercise is beneficial for hypertensive individuals who are not pregnant and may be safe for normotensive pregnant women (Type of Evidence: F), there are no data on safety in the setting of chronic hypertension and pregnancy. In view of the theoretical concerns with maintaining adequate placental blood flow in hypertensive women who are at increased risk for preeclampsia, our recommendation is to discourage aerobic exercise in hypertensive pregnant women until more data are available. Weight reduction during pregnancy, even in obese women, is not recommended. Although obesity may be a risk factor for superimposed preeclampsia, there is no evidence that limiting weight gain reduces its occurrence. Although the evidence is sparse in pregnant women, many experts recommend restriction of sodium intake to the same 2.4 g sodium intake recommended for essential hypertension. Women who already follow a more restricted sodium intake may continue to follow that dietary approach.

The use of alcohol and tobacco during pregnancy should be strongly discouraged. Both have a deleterious effect on the fetus and the mother. Excessive consumption of alcohol can cause or aggravate maternal hypertension. Tobacco is associated with a substantive risk for placental abruption and fetal growth restriction.

Treatment of Chronic Hypertension

The majority of women with chronic hypertension in pregnancy have Stage 1 to 2 hypertension (defined as systolic blood pressure of 140 to 179 mm Hg or diastolic blood pressure of 90 to 109 mm Hg) and are at low risk for cardiovascular complications within the short timeframe of pregnancy. Among women with Stage 1 to 2 preexisting essential hypertension and normal renal function, most pregnancies will have good maternal and neonatal outcomes. These women are candidates for nondrug therapy because, to date, there is no evidence that pharmacologic treatment results in improved neonatal outcomes (Type of Evidence: Ra). Since blood pressure usually falls during the first half of pregnancy, hypertension may be easier to control with less or no medication.

The value of continued administration of antihypertensive drugs to pregnant women with chronic hypertension continues to be an area of debate. Although it may be beneficial for the mother with hypertension to reduce her blood pressure, lower pressure may impair uteroplacental perfusion and thereby jeopardize fetal development (Type of Evidence: M). Although it is not generally agreed whether antihypertensive therapy is beneficial or detrimental to pregnancy outcome, several studies offer some clinical guidance. Over the past 30 years, at least seven studies have compared antihypertensive therapy with either no medication or a placebo in pregnant women with mild chronic hypertension (Type of Evidence: Pr). Higher fetal losses during the second trimester were noted among untreated women in several early trials, but this finding was not confirmed. Indeed, overall prevalence rates of these adverse outcomes were very low. In a retrospective study evaluating the course of 298 pregnant women with chronic hypertension whose antihypertensive medications had been discontinued or whose doses were reduced early in pregnancy, treatment did not decrease the frequency of superimposed preeclampsia, preterm delivery, abruptio placentae, or perinatal death when compared with untreated groups (Type of Evidence: F). Much uncertainty about the benefits of lowering blood pressure in pregnant women with mild chronic hypertension stems from published trials that are too small to detect modest reductions in obstetrical complications.

Evidence from several studies indicates the effectiveness of antihypertensive drugs in preventing exacerbation of chronic hypertension to severe hypertension during pregnancy (Type of Evidence: Ra, Pr). These trials have included heterogeneous populations of women with preexisting hypertension and gestational hypertension, different thresholds for treatment by gestational age, and the presence or absence of proteinuria, and they often included multiple treatment agents.

Most of the increased risk associated with chronic hypertension occurs in the setting of superimposed preeclampsia (Type of Evidence: F). Preeclampsia is more common in women with chronic hypertension and complicates almost 25 percent of such pregnancies. The incidence is even higher if the high blood pressure is associated with renal insufficiency, the presence of hypertension for at least 4 years, and a history of hypertension in a previous pregnancy (Type of Evidence: F). The incidence of placental abruption is markedly increased in the presence of superimposed preeclampsia (Type of Evidence: Pr).

On the basis of available data, some centers currently manage women with chronic hypertension by stopping antihypertensive medications under close observation (Type of Evidence: F, Pr). In patients with hypertension for several years, with evidence of target organ damage, or on multiple antihypertensive agents, medications may be tapered on the basis of blood pressure readings but should be continued if needed to control blood pressure. End points for reinstituting treatment include exceeding threshold blood pressure levels of 150 to 160 mm Hg systolic or 100 to 110 mm Hg diastolic or the presence of target organ damage such as left ventricular hypertrophy or renal insufficiency. Methyldopa is preferred by most practitioners. Alternatively, women who are well controlled on antihypertensive therapy before pregnancy may be kept on the same agents

(with the exception of angiotensin-converting enzyme inhibitors, AII receptor antagonists) during pregnancy.

Antihypertensive Drug Selection

While the goal of treating chronic hypertension is to reduce maternal risk, the agents selected must be efficacious and safe for the fetus, especially in regard to acute and long-range neurologic effects. Methyldopa is preferred by many physicians as first-line therapy, on the basis of reports of stable uteroplacental blood flow and fetal hemodynamics (Type of Evidence: F), and one follow-up study after 7.5 years, in a limited number of infants, showed no long-term adverse effects on development of children exposed to methyldopa in utero (Type of Evidence: F). Methyldopa causes somnolence in many individuals. If this agent cannot be tolerated, alternatives such as labetalol are selected based on more limited clinical experience. If methyldopa is ineffective, alternatives can be substituted (see below) based on rational considerations of mechanisms of action. In the latter respect, salt retention may cause refractoriness to vasodilator therapy, in which case a diuretic added to the regimen restores blood pressure control and permits prolongation of the pregnancy.

Most of the published experience with other agents comes from trials using adrenergic-blocking drugs including beta-blockers and the alpha-beta-blocker labetalol (Type of Evidence: M). There is a suggestion that beta-blockers prescribed early in pregnancy, specifically atenolol, may be associated with growth restriction (Type of Evidence: M, Re, F, Ra). On the other hand, none of these agents has been associated with any consistent ill effects; however, long-term followup studies are lacking.

Experience with calcium antagonists is limited, with most reported uses being late in pregnancy. A multicenter prospective cohort study of first trimester drug exposures reported no increase in major teratogenicity from these agents (Type of Evidence: F). A recent multicenter study randomizing patients to slow-release nifedipine or no treatment beginning in the second trimester reported neither benefits nor evidence of harm from nifedipine treatment (Type of Evidence: Ra).

The use of diuretic agents in pregnancy is controversial. The primary concern is theoretical. It is known that preeclampsia is associated with a reduction of plasma volume (Type of Evidence: F) and that fetal outcome is worse in women with chronic hypertension who fail to expand plasma volume (Type of Evidence: Ra). Whether this is a cause-and-effect relationship is not clearly established. Nonetheless, women using diuretics from early pregnancy do not increase their blood volume to the degree usually occurring in normal pregnancy (Type of Evidence: Ra). Because of the theoretical concerns, diuretics are usually not used as first-line drugs. A meta-analysis of nine randomized trials involving more than 7,000 subjects receiving diuretics revealed a decrease in the tendency of the women to develop edema and/or hypertension (Type of Evidence: M) and confirmed no increased incidence of adverse fetal effects. However, if their use is indicated, they are safe and efficacious agents, can markedly potentiate the response of other antihypertensive agents, and are not contraindicated in pregnancy except in

settings where uteroplacental perfusion is already reduced (preeclampsia and intrauterine growth restriction). Although data concerning the use of diuretics in pregnant women with essential hypertension are sparse, this working group concluded that gestation does not preclude use of diuretic drugs to reduce or control blood pressure in women whose hypertension predated conception or manifested before midpregnancy.

Angiotensin-converting enzyme inhibitors are contraindicated during pregnancy because of associations with fetal growth restriction, oligohydramnios, neonatal renal failure, and neonatal death (Type of Evidence: Pr, Re). Although no data are available on human use of angiotensin II receptor antagonists, adverse effects are likely to be similar to those reported with angiotensin converting enzyme inhibitors, and these agents should be avoided.

There are no placebo-controlled trials examining the treatment of severe hypertension in pregnancy, and none are likely to be performed, because of ethical considerations. Early reports of experience with severe chronic hypertension in the first trimester described fetal loss of 50 percent and significant maternal mortality (Type of Evidence: F). Most of the poor outcomes were in pregnancies complicated by superimposed preeclampsia (Type of Evidence: F). Antihypertensive therapy is indicated for maternal benefit but may also permit prolongation of the pregnancy and thereby improve fetal maturity.

Pregnancy, Hypertension, and Renal Disease

Among pregnant women with mild renal disease (serum creatinine less than 1.4 mg/dL), fetal survival is moderately reduced, and the underlying disease does not generally worsen (Type of Evidence: Pr). Women with renal diseases that tend to progress should be encouraged to complete their childbearing while their renal function is well preserved. The presence of hypertension before conception or early in pregnancy increases the incidence of maternal and fetal complications, with a tenfold higher relative risk of fetal loss (Type of Evidence: F, Re).

Moderate or severe renal insufficiency may accelerate during pregnancy and jeopardize fetal survival (Type of Evidence: F, Pr, Re). Hypertension occurs in more than half of these pregnancies (Type of Evidence: Pr). A decrease in birth weight correlates directly with rising maternal serum creatinine concentration (Type of Evidence: F). As renal failure progresses, the hypertension has a component of volume overload and may require sodium restriction, use of loop diuretics, or dialysis.

Recognition of superimposed preeclampsia may be difficult because proteinuria commonly increases in women with glomerular disease during pregnancy. Chronic dialysis during pregnancy is associated with significant maternal morbidity, and conception should be discouraged. Infant survival rates are higher in pregnancies where dialysis is started after conception (74 to 80 percent) than in those women who conceived while on maintenance dialysis (40 to 50 percent) (Type of Evidence: X, Re), presumably because the former are women with greater residual renal function. Infant survival

may improve with greater duration of dialysis each week. Although low birthweight and preterm delivery are the rule, prognosis appears to be improving.

Clinical note: Magnesium sulfate is hazardous in women with severe renal failure, and maintenance doses must be reduced. The usual loading dose can be given as this distributes to total body water and is not influenced by renal function. Then magnesium should be administered at a gram per hour maintenance, with therapy guided by hourly to two hourly magnesium levels until steady state is reached. Phenytoin may be considered as an alternative. (See the Anticonvulsive Therapy Section below.)

Renal transplant recipients are advised to wait 1.5 to 2 years after successful transplantation to undertake pregnancy and only if renal function is stable with creatinine of 2.0 mg/dL or less (Type of Evidence: Pr). Although pregnancies may be complicated, 92 percent of infants survive in those pregnancies that go beyond the first trimester. From the National Transplantation Pregnancy Registry, in 115 renal transplant patients who received cyclosporine, high risks to the newborn were reported in settings of maternal hypertension and serum creatinine levels greater that 1.5 mg/dL. Rates of prematurely approach 55 percent; thus, all pregnancies in transplant recipients are considered high risk (Type of Evidence: Re).

Treating Hypertension That Persists Postpartum

Women with chronic hypertension can develop encephalopathy, heart failure and pulmonary edema, and renal failure in the postpartum period. Risk factors include underlying cardiac disease, chronic renal disease, superimposed preeclampsia in the second trimester, placental abruption complicated by disseminated intravascular coagulation, and requirement for multiple antihypertensive agents (Type of Evidence: C, F). Acute hypertensive changes induced by pregnancy usually dissipate rapidly, within the first several days after delivery. Resolution of hypertension is more rapid in patients with gestational hypertension and may lag in those with preeclampsia, especially those with longer duration of preeclampsia and greater extent of renal impairment (Type of Evidence: F). This delay in resolution may reflect the time needed for endothelial recovery.

Oral antihypertensive agents may be required after delivery to help control maternal blood pressure, in particular, for women who were hypertensive before pregnancy. If prepregnancy blood pressures were normal or unknown, it is reasonable to stop oral medication after 3 to 4 weeks and observe the blood pressure at 1- to 2–week intervals for 1 month, then at 3- to 6-month intervals for 1 year. If hypertension recurs, it should be treated.

Treating Hypertension During Lactation

Breastfeeding should be encouraged and can be done safely with certain limits on antihypertensive drug choices. In mildly hypertensive mothers who wish to breastfeed for a few months, the clinician may consider withholding medication, with close monitoring of blood pressure. After discontinuation of nursing, antihypertensive therapy can be reinstituted. For patients with more

severe blood pressure elevation and taking a single antihypertensive agent, the clinician may consider reducing the dosage, then closely observing both the mother and the infant.

Little information is available regarding excretion of antihypertensive agents in human breast milk and effects on the newborn (Type of Evidence: Pr). Further, there are no data concerning long-term effects of these drugs on infants exposed through breastfeeding. The reader is referred to the text by Briggs and colleagues (Type of Evidence: Pr) and recommendations of the Committee on Drugs of the American Academy of Pediatrics (Type of Evidence: Pr). The available data suggests that all studied agents are excreted into human breast milk, although differences in the milk/plasma ratio are related to lipid solubility and extent of ionization of the drug at physiologic pH (Type of Evidence: Pr). No short-term adverse effects have been reported from exposure to methyldopa or hydralazine. Although the Committee on Drugs of the American Academy of Pediatrics considers atenolol compatible with breastfeeding, this beta-blocker, as well as metoprolol and nadolol, appears to be concentrated in breast milk. This property is not shared by propranolol or labetalol; for that reason these agents have been recommended if a beta-blocker is indicated. No data on calcium-channel blockers and lactation have been reported. Diuretics may reduce milk volume and suppress lactation. Angiotensin converting enzyme inhibitors and angiotensin receptor antagonists should be avoided on the basis of reports of adverse fetal and neonatal renal effects. Given the scarcity of data, breastfed infants of mothers taking antihypertensive agents should be closely monitored for potential adverse effects.

Fetal Assessment in Chronic Hypertension

Much of the increased perinatal morbidity and mortality associated with chronic hypertension can be attributed to superimposed preeclampsia and/or fetal growth restriction. A plan of antepartum fetal assessment is directed by these findings. Efforts should, therefore, be directed at the early detection of superimposed preeclampsia and fetal growth restriction. If these are excluded, then extensive fetal antepartum testing is less essential.

An initial sonographic assessment of fetal size and dating should be performed at 18 to 20 weeks' gestation. Fetal growth should be carefully assessed thereafter. If this is not possible with usual clinical estimation of fundal height (e.g., maternal obesity or multiple examiners), sonographic assessment should be performed at 28 to 32 weeks and monthly until term. If there is evidence of growth restriction, fetal well-being should be assessed by nonstress tests or biophysical profiles as usual for the growth-restricted fetus. Similarly, if preeclampsia cannot be excluded then fetal assessment as appropriate for the fetus of a woman with preeclampsia is mandatory. If the infant is normally grown and preeclampsia can be excluded, however, there is no indication for these studies.

IV. Preeclampsia

Prevention of Preeclampsia

The ability to prevent preeclampsia is limited by lack of knowledge of its underlying cause. Prevention has focused on identifying women at high risk, followed by close clinical and laboratory monitoring to recognize the disease process in its early stages. These women can then be selected for more intensive monitoring or delivery. Although these measures do not prevent preeclampsia, they may be helpful for preventing some adverse maternal and fetal sequelae.

Use of Low-Dose Aspirin To Prevent Preeclampsia: Benefits of low-dose aspirin prophylaxis are unproven for most women, including nulliparas. The prevailing opinion is that women without risk factors do not benefit from treatment, despite earlier prospective studies that suggested that aspirin administration reduced the incidence of preeclampsia. The basis for this opinion is the results of eight large trials in different populations around the world. Overall, the results of these trials, which included more than 27,000 pregnant women, demonstrate minimal to no reduction in the incidence of preeclampsia with low-dose aspirin (Type of Evidence: Ra, Pr).

An important study on low-dose aspirin prophylaxis in 2,539 women at higher risk for preeclampsia was published recently by the National Institutes of Health (NIH) (Type of Evidence: Ra). Included were four subgroups of women with pregestational insulin-treated diabetes mellitus, chronic hypertension, multifetal gestation, or preeclampsia in a previous pregnancy. The incidence of preeclampsia, perinatal death, preterm delivery, and fetal growth restriction was the same in the aspirin- and placebo-treated patients, with no significant differences in outcomes for any of the four subgroups at higher risk.

Calcium Supplementation: There are no data indicating that dietary supplementation with calcium will prevent preeclampsia in low-risk women in the United States. Certainly, a diet that provides 1,000 mg elemental calcium daily is recommended for general health (Type of Evidence: Pr). Whether an enriched calcium diet beyond this amount may have benefit is unproven.

Results from a large National Institutes of Health (NIH) trial in 4,589 healthy nulliparous women randomized at 13 to 21 weeks to 2 g elemental calcium daily or placebo indicate that calcium supplementation neither reduced the incidence or severity of preeclampsia nor delayed its onset (Type of Evidence: Ra). There were no differences in the prevalence of nonproteinuric hypertension. Even within the subgroup of women with the lowest quintile of dietary calcium intake, similar to that reported for women in many developing countries, no benefit of calcium supplementation was demonstrated (Type of Evidence: Ra).

Still, randomized trials of calcium supplementation in nulliparous women considered at high risk demonstrated significant reductions in incidence of preeclampsia (Type of Evidence: Ra).

Other Dietary Supplements: Prophylactic magnesium supplementation has not been shown to be beneficial in preventing preeclampsia (Type of Evidence: Ra). The results of three randomized trials of fish oil supplementation in women at high risk for preeclampsia revealed no

reduction in incidence of preeclampsia (Type of Evidence: Ra). A recent study showing the benefits of vitamins C and E to prevent preeclampsia was encouraging but needs further confirmation (Type of Evidence: Ra).

Management of Preeclampsia: Rationale for Treatment

The objectives of therapy for preeclampsia are based on a philosophy of management arising from the knowledge of the pathology, pathophysiology, and prognosis of the disorder for mother and baby. The following three important tenets underlie management schemes:

1. Delivery is always appropriate therapy for the mother but may not be so for the fetus. For maternal health, the goal of therapy is to prevent eclampsia as well as other severe complications of preeclampsia. These disorders are completely reversible and usually begin to abate with delivery. Thus, if only maternal well-being was considered, the delivery of all women with preeclampsia, regardless of the severity of preeclampsia or duration of gestation, would be appropriate. Conversely, delivery induction is not indicated for a preterm fetus with no evidence of fetal compromise in women with mild disease. There are two important corollaries of this statement. First, any therapy for preeclampsia other than delivery must have as its successful end point the reduction of perinatal morbidity and mortality. Second, the cornerstone of obstetric management of preeclampsia is based on whether the fetus is more likely to survive without significant neonatal complications in utero or in the nursery.
2. The pathophysiologic changes of severe preeclampsia indicate that poor perfusion is the major factor leading to maternal physiologic derangement and increased perinatal morbidity and mortality. Attempts to treat preeclampsia by natriuresis or by lowering blood pressure may exacerbate the important pathophysiologic changes.
3. The pathogenic changes of preeclampsia are present long before clinical diagnostic criteria are manifest. Several studies indicate that changes in vascular reactivity, plasma volume, and renal tubular function antedate, in some cases by weeks, the increases in blood pressure, protein excretion, and sodium retention. These findings suggest that irreversible changes affecting fetal well-being may be present before the clinical diagnosis. If there is a rationale for management other than delivery, it would be to palliate the maternal condition to allow fetal maturation and cervical ripening.

Nonpharmacological Management

4. Fetal Evaluation

Fetal surveillance is indicated for the woman with preeclampsia. (See the section titled "High-Risk Patients Presenting With Normal Blood Pressure.")

Nonstress testing, ultrasound assessment of fetal activity and amniotic fluid volume (biophysical profile), and fetal movement counts constitute the most common fetal surveillance techniques. If determination of pulmonary maturity would influence management,

amniocentesis should be done to determine this before the interruption of pregnancy.

For all women with preeclampsia, daily fetal movement assessment is a useful screening assessment. More formal testing is indicated if movements are not normal. Formal testing (nonstress testing, biophysical profile) should be performed periodically with even normal fetal activity. The frequency of formal testing will be dictated by the clinical condition. Although weekly to biweekly assessment will usually suffice, for women with severe preeclampsia who are being managed expectantly, daily testing is appropriate. (See Table 2 below.) If possible fetal compromise is indicated by fetal surveillance, then decision-making for delivery requires judgment heavily weighted by fetal age.

e 2. Fetal Monitoring in Gestational Hypertension and Preeclampsia
ational Hypertension ertension only without proteinuria, with normal laboratory test results, and without symptoms)
Estimation of fetal growth and amniotic fluid status should be performed at diagnosis. f results are normal, repeat testing only if there is significant change in maternal condition. Nonstress test (NST) should be performed at diagnosis. If nonstress test is ionreactive, perform biophysical profile (BPP). If biophysical profile value is eight or if nonstress test s reactive, repeat testing only if there is significant change in maternal condition.
Preeclampsia hypertension, normal platelet count, normal liver enzyme values, and no maternal symptoms)
Estimation of fetal growth and amniotic fluid status should be performed at diagnosis. f results are normal, repeat testing every 3 weeks. Nonstress test, biophysical profile, or both should be performed at diagnosis. If ionstress test is reactive or if biophysical profile value is eight, repeat weekly. Testing should be epeated immediately if there is abrupt change in maternal condition. If estimated fetal weight by ultrasound is less than the 10th percentile for gestational ıge or if there is oligohydramnios (amniotic fluid index=5 cm), then testing should be performed at east twice weekly.

5. Maternal Evaluation

Antepartum monitoring has two goals. The first is to recognize preeclampsia early; the second is to observe progression of the condition, both to prevent maternal complications by delivery and to determine whether fetal well-being can be safely monitored with the usual intermittent observations.

At present, clinical management of preeclampsia is directed by overt clinical signs and symptoms. Although rapid weight increase and facial edema may indicate the fluid and sodium retention of preeclampsia, they are neither universally present nor uniquely characteristic of preeclampsia. These signs are, at most, a reason for closer monitoring of blood pressure and urinary protein. Early recognition of impending preeclampsia is based primarily on blood pressure increases in the late second and early third trimesters. Once blood pressure starts to rise (this may be the first sign of developing preeclampsia), a repeat examination within 1 to 3 days is recommended. In selected patients blood pressure and urinary protein may be checked at home. In either case, the woman should be evaluated for symptoms suggestive of preeclampsia (e.g., headaches, blurred vision, right upper quadrant or epigastric pain) and should undergo laboratory testing for platelet count, renal function, and liver enzymes. Quantification of a 12- to 24-hour urine sample for proteinuria is recommended. (See Table 1 above.) These measurements determine how fast the condition is progressing to ensure that it is not following a fulminant course. The frequency of subsequent observations is determined by the initial observations and the ensuring clinical progression. If the condition appears stable, weekly observations may be appropriate. The initial appearance of proteinuria is an especially important sign of progression and dictates frequent observations.

Often, hospitalization is initially recommended for women with new-onset preeclampsia. After maternal and fetal conditions are serially assessed, subsequent management may be continued in-hospital, at a day-care unit, or at home on the basis of the initial assessment. Prolonged hospitalization for the duration of pregnancy allows rapid intervention in case of fulminant progression to hypertensive crisis, eclampsia, or abruptio placentae (Type of Evidence: Pr). These complications are rare in compliant women who have mild hypertension, minimal proteinuria, no symptoms, and normal platelet counts and serum liver enzyme levels. Recently, ambulatory management at home or at a day-care unit has been evaluated as an option for monitoring women with mild gestational hypertension or preeclampsia remote from term. A number of observational and randomized studies suggest a place for ambulatory management of selected women. If day care or home management is selected, it should include frequent maternal and fetal evaluation and access to health care providers (Type of Evidence: Pr). If worsening of preeclampsia is diagnosed, as determined by laboratory findings, symptoms, and clinical signs, hospitalization is indicated.

Hospitalization for the duration of pregnancy is indicted for preterm onset of severe gestational hypertension or preeclampsia. The decision to prolong the pregnancy in these women is determined day by day. The women should receive intensive maternal and fetal surveillance, usually at a tertiary care facility (Type of Evidence: F, Ra). Laboratory studies are performed at frequent intervals and include serial determinations of platelet count, serum liver enzyme levels, renal function, and urinary protein. Assiduous attention is given for

worsening hypertension; evidence of central nervous system involvement that includes severe headache, disorientation, or visual symptoms; and hepatic involvement indicated by epigastric pain and tenderness.

Antepartum Management of Preeclampsia

There is little to suggest that any therapy alters the underlying pathophysiology of preeclampsia. Therapeutic efforts that may be palliative, slow progression of the disorder, and permit continuation of pregnancy have not been shown to reverse the underlying disorder. Restricted activity is a usual and reasonable recommendation for women with preeclampsia, although its efficacy is not clearly established. Strict sodium restriction and diuretic therapy appear to have no role in management. Finally, results of several randomized trials suggest that antihypertensive therapy for women with gestational hypertension or preeclampsia does not improve perinatal outcomes (Type of Evidence: Ra, Pr).

Indications for Delivery

Delivery is the only definitive treatment for preeclampsia, and some suggested indications are listed in Table 3 below.

Table 3. Indications for Delivery in Preeclampsia*

Maternal	Fetal
Gestational age ≥38 weeks	Severe fetal growth restriction
Platelet count <100,000 cells/mm^3	Nonreassuring fetal testing results
Progressive deterioration in hepatic function	Oligohydramnios
Progressive deterioration in renal function	
Suspected abruptio placentae	
Persistent severe headaches or visual changes	
Persistent severe epigastric pain, nausea, or vomiting	

*Delivery should be based on maternal and fetal conditions as well as gestational age.

All women with this diagnosis should be considered for delivery at 40 weeks' gestation. Delivery may be indicated for women with mild disease and a favorable cervix for induction at 38 weeks' gestation and should be considered in women who have severe preeclampsia beyond 32 to 34 weeks' gestation. At gestational week 33 to 34, the fetus may benefit from corticosteroid administration.

Prolonged antepartum management in women with severe preeclampsia is possible in a select group of women with fetal gestational age between 23 and 32 weeks. In some women, preeclampsia improves after hospitalization and treatment with magnesium sulfate and antihypertensive agents given acutely (Type of Evidence: Ra). Such management may prolong pregnancy, with a decrease in perinatal morbidity and mortality. It should be attempted only in centers equipped to provide close maternal and fetal surveillance (Type of Evidence: Pr). Delivery in these preterm pregnancies is indicated by worsening maternal symptoms, laboratory evidence of end-organ dysfunction, or fetal deterioration.

Route of Delivery

Vaginal delivery is preferable to cesarean delivery for women with preeclampsia, thus avoiding the added stress of surgery to multiple physiologic aberrations. Acute palliation for several hours does not increase maternal risk if performed appropriately. Labor induction should be carried out aggressively once the decision for delivery is made. In gestation remote from term in which delivery is indicated and with fetal maternal conditions stable enough to permit pregnancy to be prolonged 48 hours, glucocorticoids can be safely administered to accelerate fetal pulmonary maturity. (See Table 3 above.)

The aggressive approach to induction includes a clear end point for delivery, usually within 24 hours of the decision to induce labor. Most experts recommend a trial of induction regardless of cervical condition. If vaginal delivery cannot be effected within a reasonable time, cesarean delivery is considered and is also performed for other usual obstetrical indications.

Neuraxial (epidural, spinal, and combined spinal epidural) techniques offer many advantages for labor analgesia and can be safely administered to the preeclamptic parturient. Dilute epidural infusions of local anesthetic plus opioid produce adequate sensory block without motor block or clinically significant sympathectomy. When neuraxial techniques are used for cesarean delivery, however, there is a possibility of extensive sympatholysis with profound hypotension which may lead to decreased cardiac output and further diminished uteroplacental perfusion. This may be more likely with single-shot spinal anesthesia, which although considered acceptable by some experts, is still considered by others to be relatively contraindicated in women with severe preeclampsia. A recent analysis, however, suggests that spinal anesthesia can be used safely in the severely preeclamptic patient undergoing cesarean section, since the magnitude of maternal blood pressure declines appear to be similar after spinal or epidural anesthesia (Type of Evidence: Re). Hypotension can usually be avoided by meticulous attention to anesthetic technique and careful volume expansion. In one unblinded study of 80 women

with severe preeclampsia randomized to receive epidural, combined spinal-epidural, or general anesthesia, all three regimens appeared equally safe (Type of Evidence: Ra).

With general anesthesia, significant hypertension may occur at the time of laryngoscopy and tracheal intubation and again during emergence and extubation. These responses can usually be blocked by appropriate pretreatment with hydralazine, nitroglycerin, or labetalol. Airway edema may be seen in the preeclamptic patient and may increase the risks of a "difficult airway" situation leading to failed intubation and ventilation. Because general anesthesia poses considerably greater risk to parturients than regional anesthesia (Type of Evidence: X), the risk of a failed intubation must be weighed against the risk of transient hypotension when deciding between general and regional anesthesia for cesarean section in the severely preeclamptic/eclamptic patient. Although neuraxial techniques have become the preferred method to provide labor analgesia or anesthesia for cesarean section in women with severe preeclampsia-eclampsia, they are relatively contraindicated in the presence of coagulopathy. Early consultation with an anesthesiologist is suggested for parturients with severe preeclampsia.

Anticonvulsive Therapy

Anticonvulsive therapy is usually indicated either to prevent recurrent convulsions in women with eclampsia or to prevent convulsions in women with preeclampsia. There is universal agreement that women with eclampsia should receive anticonvulsive therapy (Type of Evidence: Ra). Anticonvulsive therapy is usually indicated either to prevent recurrent convulsions in women with eclampsia or to prevent convulsions in women with preeclampsia. There is universal agreement that women with eclampsia should receive anticonvulsive therapy (Type of Evidence: Ra). Several randomized studies indicate that parenteral magnesium sulfate reduced the frequency of eclampsia more effectively than phenytoin in a mixed group of gestational hypertensive and preeclamptic women (Type of Evidence: Pr, M). Parenteral magnesium sulfate is given during labor, delivery, and for variable durations postpartum. There is not clear agreement concerning the use of prophylactic magnesium sulfate for women with preeclampsia (Type of Evidence: Ra). The results of two large randomized trials showed that parenteral magnesium sulfate reduces the frequency of eclampsia in women with either pregnancy-induced hypertension or severe preeclampsia (Type of Evidence: Ra). Although parenteral magnesium sulfate should be given peripartum to women with severe preeclampsia, its benefits with mild gestational hypertension or preeclampsia remain unclear. A multicenter randomized trial to answer this question is urgently needed. Precautions regarding the use of magnesium sulfate during pregnancy in women with renal failure are discussed in the section on Pregnancy, Hypertension, and Renal Disease.

Invasive Hemodynamic Monitoring

Some investigators recommend the use of invasive hemodynamic monitoring in managing women with severe preeclampsia-eclampsia. It has been used to monitor fluid therapy during plasma volume expansion (Type of Evidence: Re); in managing women with pulmonary edema, persistent oliguria

unresponsive to fluid challenge, and intractable severe hypertension; and in some patients receiving epidural anesthesia (Type of Evidence: Pr). There is no published evidence that the use of invasive hemodynamic monitoring is indicated for the purposes mentioned above.

Treatment of Acute Hypertension

Antihypertensive therapy is indicated when blood pressure is dangerously high or rises suddenly in women with preeclampsia, especially intrapartum. Antihypertensive agents can be withheld as long as maternal pressure is only mildly elevated. Some experts would treat persistent diastolic levels of 105 mm Hg or higher. Others would withhold treatment until diastolic blood pressure levels reach 110 mm Hg (Type of Evidence: Pr). In adolescents whose diastolic pressures were recently below 75 mm Hg, treating persistent levels of 100 mm Hg or higher may be considered. When treatment is required the ideal drug that reduces pressures to a safe level should act quickly, reduce pressure in a controlled manner, not lower cardiac output, reverse uteroplacental vascular constriction, and result in no adverse maternal or fetal effects. The medications used to treat hypertensive crises in pregnancy, and their route of administration, are summarized in Table 4 below. Details of their pharmacology and safety are discussed elsewhere (Type of Evidence: Pr).

The most commonly used drug is hydralazine, administered either intravenously (IV) or intramuscularly (IM), which, if given cautiously, is successful in most instances. It has been shown to be effective against preeclamptic hypertension. Although this drug is sometimes given as an intravenous infusion, the pharmacokinetics (maximal effect at 20 minutes, duration of action 6 to 8 hours) indicate intermittent bolus injections are more sensible. A 5 mg bolus is given intravenously over 1 to 32 minutes. After 20 minutes, subsequent doses are dictated by the initial response. Once the desired effect is obtained, the drug is repeated as necessary (frequently in several hours) (Type of Evidence: Re). Parenteral labetalol has been shown to be effective for the treatment of acute severe hypertension in pregnancy (Type of Evidence: M, F). The drug may be used as intravenous bolus injections of 20 mg or 40 mg, or as continuous intravenous infusion of 1 mg/kg as needed. Labetalol is usually used as a second-line drug. It should be avoided in women with asthma and in those with congestive heart failure.

The use of oral nifedipine has been described in a limited number of women with acute severe hypertension during pregnancy (Type of Evidence: F). Details of these reports are summarized elsewhere (Type of Evidence: Pr). Nifedipine acts rapidly, causing significant reduction in arterial blood pressure within 10 to 20 minutes of oral administration. Although it has favorable hemodynamic effects (Type of Evidence: F), physicians should be advised that rapidly acting nifedipine (in capsules containing the liquid form) has never been approved by the United States Food and Drug Administration (FDA) for treating hypertension or hypertensive emergencies. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (Type of Evidence: Pr) has recommended that it not be used for this purpose because it has been associated with fatal and nonfatal untoward cardiovascular events, especially in older patients

(Type of Evidence: Pr). Of 16 case reports previously reviewed (Type of Evidence: Pr), one was a 37-year-old pregnant woman whose blood pressure was reduced from 150/118 to 90/55, precipitating the need for cesarean section because of fetal distress. Care should be exercised when using nifedipine or any calcium antagonist with magnesium sulfate (Type of Evidence: Pr).

In the rare case, sodium nitroprusside may be indicated after the failure of hydralazine, nifedipine and labetalol for acute hypertensive emergency.

Treatment of Acute Severe Hypertension in Preeclampsia*

mm Hg systolic and/or =105 mm Hg diastolic if sustained

Hydralazine: Start with 5 mg intravenously (IV) or 10 mg intramuscularly (IM). If blood pressure controlled, repeat at 20-minute intervals (5 to 10 mg depending on response). Once blood ure control is achieved, repeat as needed (usually about 3 hours). If no success by 20 mg venous or 30 mg intramuscular total, consider another drug.

Labetalol: Start with 20 mg intravenously as a bolus; if effect is suboptimal, then give 40 mg 10 tes later and 80 mg every 10 minutes for two additional doses. Use a maximum of 220 mg. If ed blood pressure levels are not achieved, switch to another drug. Avoid giving labetalol to women asthma or congestive heart failure.

Nifedipine: Start with 10 mg orally and repeat in 30 minutes if necessary. See precautions, in ment of Acute Hypertension section. (Short-acting nifedipine is not approved by United States Food Drug Administration [FDA] for managing hypertension.)

Sodium nitroprusside is rarely needed for hypertension not responding to the drugs listed above or if there are clinical findings of hypertensive encephalopathy. Start at a rate of 0.25 grams/kg/min to a maximum dose of 5 micrograms/kg/min. Fetal cyanide poisoning may occur if for more than 4 hours.

fects: See Physicians Desk Reference (53rd edition).

Sudden and severe hypotension can result from the administration of any of these agents, short-acting oral nifedipine. The goal of blood pressure reduction in emergency situations should ual reduction of blood pressure to the normal range. (See Treatment of Acute Hypertension

Note: In managing hypertensive emergencies, the intravenous (IV) route is safer than oral or cular (IM) administration because it is easier to combat inadvertent hypotension by stopping an us injection or infusion than it is to stop intestinal or intramuscular absorption of an orally or cularly-administered drug.

V. Postpartum Counseling and Followup

Women who develop hypertension during pregnancy should be carefully reevaluated during the immediate postpartum months and counseled with respect to future gestations and remote cardiovascular risks as well. Any laboratory abnormality or physical finding that has not returned to normal before post delivery discharge should be reassessed at postpartum follow-up.

The expectation is that hypertension and other signs or symptoms or organ dysfunction associated with preeclampsia will have remitted by the 6-week postpartum examination, but if abnormalities persist, the patients should be reexamined 6 weeks later, when persisting pathology will probably be chronic.

Counseling for Future Pregnancies

Women who have had preeclampsia are more prone to hypertensive complications in subsequent pregnancies. Risk is best established for nulliparas with a history of preeclampsia, the magnitude of the recurrence rate increasing the earlier the disease manifested during the index pregnancy. For instance, when preeclampsia presents clinically before gestational week 30, the recurrence rate may be as high as 40 percent (Type of Evidence: F). Preeclampsia reappearance rates may also be population-specific. For example, in white woman with well-defined disease after gestational week 36, recurrence is barely 10 percent (Type of Evidence: Pr), but it may be substantially greater in black patients (Type of Evidence: F). The recurrence rate for women with one episode of HELLP is almost 5 percent (Type of Evidence: F).

Recurrence rates are higher for those experiencing preeclampsia as multiparas compared with nulliparous women (Type of Evidence: Re). Risk is also increased in multiparas who conceive with a new father even when their first pregnancy was normotensive, the incidence being intermediate between that of primiparous women and monogamous multiparous women who have not had a preeclamptic pregnancy (Type of Evidence: Re).

Of interest are data indicating that women with early-onset severe preeclampsia harbor metabolic abnormalities or risk factors associated with vascular thrombosis. These include activated protein C resistance (Factor V Leiden), antiphospholipid antibodies, hyperhomocysteinemia, and protein S deficiency (Type of Evidence: F, Re). Therefore, patients with a history of early-onset severe preeclampsia should be evaluated for evidence of prior thromboembolic diseases and, if they have such a history, should be tested for the above-described abnormalities (which when present jeopardize not only future pregnancies but the patients' general health as well).

Remote Cardiovascular Prognosis – Preeclampsia-Eclampsia

The remote prognosis of women experiencing preeclampsia or eclampsia is best summarized as follows; the more certain the diagnosis is preeclampsia alone (e.g., nulliparity, especially if complicated by eclampsia or confirmed by renal biopsy), the lower the prevalence of remote cardiovascular disorders. Prevalence of remote hypertension, however, is increased in nulliparous women with preeclampsia or eclampsia manifesting hypertension in subsequent gestations, multiparas who develop the disorder, and women with severe early-onset disease of any parity. The literature further suggests that preeclampsia-eclampsia, by itself, is not a cause of essential hypertension. In essence, it is the hypertension in subsequent gestations, presence of preeclampsia in a multipara, or early-onset disease in any pregnancy that signals that the disease has occurred in a patient with an increased probability of essential hypertension later in life (Type of Evidence: Ra, F, Pr).

In summary, it is reasonable to counsel patients as follows: If preeclampsia occurred late in an initial gestation, there is no evidence of remote cardiovascular risk, but subsequent pregnancies will help us define risk more accurately. Women with early-onset disease, multiparous women with preeclampsia or only hypertension, and those manifesting gestational hypertension in any pregnancy are at increased cardiovascular risk - information of importance for long-term health care strategies. The best news, however, is that women experiencing normotensive births have a reduced risk for remote hypertension.

Type of supporting evidence

M: Meta-analysis; an analysis of a compendium of experimental studies

Ra: Randomized controlled trials; also known as experimental studies

Re: Retrospective analyses; also know as case-control studies

F: Prospective followup; also known as cohort studies, including historical cohort studies and long-term followup

X: Cross-sectional population studies; also known as prevalence studies

Pr: Previous review or position statements

C: Clinical interventions (nonrandomized)

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is stated for selected recommendations (see the "Major Recommendations" section).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Effective diagnosis and treatment of hypertensive disorders in pregnant women, including chronic hypertension, preeclampsia-eclampsia, and gestational hypertension, resulting in decreased maternal and fetal morbidity and mortality.

POTENTIAL HARMS

- Methyldopa causes somnolence in many individuals.

- Sudden and severe hypotension can result from the administration of hydralazine, labetalol, sodium nitroprusside, and especially nifedipine.
- There is a suggestion that beta-blockers prescribed early in pregnancy, specifically atenolol, may be associated with growth restrictions.
- Angiotensin-converting enzyme inhibitors are contraindicated during pregnancy because of associations with fetal growth restrictions, neonatal renal failure, and neonatal death.
- For the rare occasions when sodium nitroprusside is used, fetal cyanide poisoning may occur if it is used for more than 4 hours.

Subgroups Most Likely to Be Harmed:

- Rapidly acting nifedipine has been associated with fatal and nonfatal untoward cardiovascular events, especially in older patients.
- Avoid giving labetalol to women with asthma or congestive heart failure.
- Magnesium sulfate is hazardous in women with severe renal failure, and maintenance doses must be reduced.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

The members of the working group recognize that the responsible clinician's judgment of the individual patient's needs remains paramount. Therefore, this national guideline should serve as a tool to be adapted and implemented in individual situations.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Heart Lung and Blood Institute. National High Blood Pressure Education Program: Working Group Report on High Blood Pressure in Pregnancy. Bethesda (MD): National Heart, Lung and Blood Institute (NHLBI); 2000 Jul. 38 p. [201 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1990 (revised 2000 Jul)

GUIDELINE DEVELOPER(S)

National Heart, Lung, and Blood Institute (U.S.) - Federal Government Agency [U.S.]
National High Blood Pressure Education Program - Federal Government Agency [U.S.]

SOURCE(S) OF FUNDING

United States Government

GUIDELINE COMMITTEE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

ENDORSER(S)

Agency for Healthcare Research and Quality - Federal Government Agency [U.S.]
American Academy of Family Physicians - Medical Specialty Society
American Academy of Insurance Medicine - Professional Association
American Academy of Neurology - Medical Specialty Society

American Academy of Ophthalmology - Medical Specialty Society
American Academy of Physician Assistants - Professional Association
American Association of Occupational Health Nurses - Professional Association
American College of Cardiology Foundation - Medical Specialty Society
American College of Chest Physicians - Medical Specialty Society
American College of Occupational and Environmental Medicine - Medical Specialty Society
American College of Physicians - Medical Specialty Society
American College of Preventive Medicine - Medical Specialty Society
American Dental Association - Professional Association
American Diabetes Association - Professional Association
American Dietetic Association - Professional Association
American Heart Association - Professional Association
American Hospital Association - Professional Association
American Medical Association - Medical Specialty Society
American Nurses Association - Professional Association
American Optometric Association - Professional Association
American Osteopathic Association - Professional Association
American Pharmacists Association - Professional Association
American Podiatric Medical Association - Medical Specialty Society
American Public Health Association - Professional Association
American Red Cross - Private Nonprofit Organization
American Society of Health-System Pharmacists - Professional Association
American Society of Hypertension - Disease Specific Society
Association of Black Cardiologists - Medical Specialty Society
Citizens for Public Action on High Blood Pressure and Cholesterol Inc - Private Nonprofit Organization
Department of Veterans Affairs - Federal Government Agency [U.S.]
Health Care Financing Administration - Federal Government Agency [U.S.]
Health Resources and Services Administration - Federal Government Agency [U.S.]
International Society on Hypertension in Blacks - Disease Specific Society
National Black Nurses Association, Inc - Professional Association
National Hypertension Association, Inc - Disease Specific Society
National Institute of Diabetes and Digestive and Kidney Diseases (U.S.) - Federal Government Agency [U.S.]
National Kidney Foundation - Disease Specific Society
National Medical Association - Professional Association
National Optometric Association - Professional Association
National Stroke Association - Professional Association
NHLBI Ad Hoc Committee on Minority Populations
Society for Nutrition Education - Professional Association
Society of Geriatric Cardiology - Professional Association

GUIDELINE STATUS

This is the current release of the guideline. This guideline updates the 1990 guideline titled "National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Pregnancy" (Bethesda [MD]: National High Blood Pressure Education Program, National Heart, Lung, and Blood Institute, National Institutes of Health, 1990).

An update is not in progress at this time.

GUIDELINE AVAILABILITY

Electronic copies: Available from the National Heart, Lung, and Blood Institute's Web site.

Print copies: Available from NHLBI Information Center, P.O. Box 30105, Bethesda, MD 20824-0105; e-mail: nhlbicc@dgsys.com.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

The following is available:

- High blood pressure in pregnancy. Bethesda, MD: National High Blood Pressure Education Program, National Heart, Lung, and Blood Institute, National Institutes of Health.

Available from the National Heart, Lung and Blood Institute Web site.

Print copies: Available from NHLBI Information Center, P.O. Box 30105, Bethesda, MD 20824-0105; e-mail: nhlbiic@dgsys.com

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

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